Manuela E. Kaufmann[1*]
Patrik Lenherr[2*]
Clemens Walter[3]
Daniel B. Wiedemeier[4]
Thomas Attin[1]
Patrick R. Schmidlin[1]

[1] Clinic of Conservative and Preventive Dentistry, Center of Dental Medicine, University of Zurich, Zurich, Switzerland
[2] Private practice, Zahnmedizin Wiesental, Herisau, Switzerland
[3] Department of Periodontology, Endodontology and Cariology, University Centre for Dental Medicine, University of Basel, Basel, Switzerland
[4] Statistical Services, Center of Dental Medicine, University of Zurich, Zurich, Switzerland

* Both authors contributed equally to this manuscript and share first authorship

CORRESPONDENCE
Dr. med. dent.
Manuela Kaufmann
Universität Zürich
Zentrum für Zahnmedizin
Klinik für Zahnerhaltung und Präventivzahnmedizin
Bereich Parodontologie und peri-implantäre Erkrankungen
Plattenstrasse 11
CH-8032 Zürich
Tel. +41 44 634 33 04
E-mail: manuela.kaufmann@zzm.uzh.ch

SWISS DENTAL JOURNAL SSO 130: 572–583 (2020)
Accepted for publication: 10 January 2020

Systemically administered amoxicillin/metronidazole versus azithromycin as adjuncts to subgingival instrumentation during non-surgical periodontal therapy

A systematic review

KEYWORDS
Systematic review
Azithromycin
Macrolide, amoxicillin
Metronidazole
Aggressive periodontitis
Chronic periodontitis
Nonsurgical therapy
Clinical, in vivo

SUMMARY

The aim of this systematic review was to compare the combination of amoxicillin and metronidazole or azithromycin when used as adjunct systemic antibiotics during the non-surgical periodontal therapy of chronic periodontitis. The databases Medline, Embase, Cochrane and Biosis were electronically searched. Additionally, a hand search was conducted up to24 October 2019. From 76 papers, only two papers could be included in the analysis. The calculated mean probability of having probing depth (PD) ≤3 mm after non-surgical periodontal therapy in moderate (4–6 mm) and deep (>6 mm) pockets accounted for 7% and 6% for the combination of amoxicillin and metronidazole. For azithromycin it was 3% and 1%, respectively. The mean probability of persisting pockets ≥5 mm was 0 for moderate pockets with both antibiotic therapies whereas for deep pockets therapy with amoxicillin and metronidazole seems slightly lower. On the basis of two studies included in this systematic review, azithromycin as an adjunct to scaling and root planing in the non-surgical adjunctive treatment of chronic periodontitis seems to provide clinical results similar to the combination of amoxicillin and metronidazole. On behalf of patients' compliance and well-being, the use of azithromycin as an adjunct to non-surgical periodontal therapy of chronic periodontitis may be a substitute to amoxicillin and metronidazole. However, interpretation should be taken with caution, since the results are based on two studies only; thus, further clinical trials are necessary to underline or refute this trend.

Introduction

Periodontitis is characterised by gingival inflammation, formation of gingival pockets, progressive attachment, and bone loss. The standard therapy in a first step is scaling and root planing (SRP) (Badersten et al. 1981). The use of adjunctive systemic antibiotics has been shown to allow for significant benefits in reducing periodontal probing depths (PD), supporting the regain of clinical attachment levels (CAL) and reducing the risk of further attachment loss (AL) (Badersten et al. 1984).

A recent systematic review evaluated the efficacy of different antibiotics in the context of a non-surgical therapy of chronic periodontitis (CP) patient (Keestra et al. 2015). All antibiotic regimens were able to significantly reduce pocket depth formation in moderate and deep pockets after three §months and no specific antibiotic seemed more effective in this aspect. However, a trend showed that metronidazole (MTZ) or amoxicillin (AMX) combined with MTZ resulted in better clinical improvements than doxycycline (DOX) or azithromycin (AZM), which became smaller after one year. Another systematic review focussed on AZM alone (Buset et al. 2015). In accordance with Keestra et al. (Keestra et al. 2015), this review also elaborated that there was no data available underlining any clinical superiority of AZM when compared to AMX + MTZ (Buset et al. 2015). The authors concluded therefore that AZM should be mainly prescribed as an alternative in cases where the combination of AMX + MTZ is not well tolerated. Noteworthy, both reviews only included studies comparing these different regimens directly.

Accordingly, the present review aimed to compare the efficacy of the combination of AMX + MTZ versus AZM concerning PDs of CP patients who underwent non-surgical therapy. We hypothesised that there is no difference between the two treatment regimens.

Material and methods

The study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews (Shamseer et al. 2015). Conforming to the PICO (Population, Intervention, Comparison, and Outcome) criteria for comparing clinical studies, the focused question was adjusted as follows (Forrest & Miller 2002):

"What is the in-vivo efficacy of AMX + MTZ as compared to AZM in non-surgical periodontal therapy concerning PD after therapy in CP patients?"

Primary outcome was pocket depth, secondary outcomes were not considered.

Search strategy

A literature search was performed in the *U.S. National Library of Medicine (Medline), Excerpta Medical Database (Embase), Biosis Previews Database,* and the *Cochrane Central Library*. Articles were included up to 24 October 2019. The following search terms and keywords were considered in the present research:
(azithromycin) OR (zithromax)
AND
(metronidazole AND amoxicillin) OR ("van winkelhoff")
AND
(periodontitis) OR (periodontal)
including the according MeSH terms respectively.
Also, a hand search of the reference lists of the evaluated studies concerning the topic was performed.

Study selection

The titles and abstracts of the papers were double-checked for possible inclusion by two independent authors (PL and MK). All potentially eligible studies were ordered and their full texts were assessed. The final decision about the inclusion of all studies was made by mutual agreement as well as consultation with a third author (PRS).

Eligibility criteria for studies

Only randomised controlled clinical trials (RCTs), which compared AMX + MTZ versus AZM in non-surgical periodontal therapy of CP were considered. Only articles published in English or German were included in this review. Articles appearing in more than one database were considered only once (Fig. 1).

Risk of bias

All full texts, which satisfied the eligibility criteria, were evaluated by two researchers independently (PL and MK) for methodological risk of bias. The methodology followed is, according to the Cochrane Collaboration standard scheme for bias: selection, performance, attrition, detection, and reporting bias (Zeng et al. 2015). Disagreements were resolved again by discussion, and a third person was consulted if required (PRS).

The overall risk of bias was classified as low, unclear, or high. The researchers have defined six critical domains for the risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. When the study was judged as "unclear" in one essential domain, the authors of the article in question were contacted for additional information. Two criteria were considered for the classification of "other bias", i.e. sample calculation and location and date of the study.

Data extraction

Excluded articles were classified hierarchically, and explanations for exclusion were provided individually (see Tab. IV in the Appendix). The following data were extracted: PD given as means or medians at baseline, including the respective standard deviations or 5th and 95th percentiles. Data were included after three or six months, if available. The study also aimed to attain the original raw data of the selected paper contacting the authors. Raw data could not be shared because of proprietary material as well as due to privacy reasons.

Statistics

All calculations were performed with the statistical software R (Team 2015). Based on the mean baseline PDs and their standard deviation, the probability of remaining PDs after therapy with different cut-off values (i.e. ≤3 mm or >5 mm) in both antibiotic protocols were calculated based on the approach suggested by Hauri et al. (Hauri et al. 2008). This approach may work well when the underlying data is approximately normally distributed. Thus, the study only applied it on the published data from Saleh et al. (Saleh et al. 2016), since it seems likely that such an approach would not satisfactorily capture the data from Jentsch et al. (Jentsch et al. 2016). The present research abstained from conducting a meta-analysis because such calculations do not seem very meaningful when only two studies can be included.

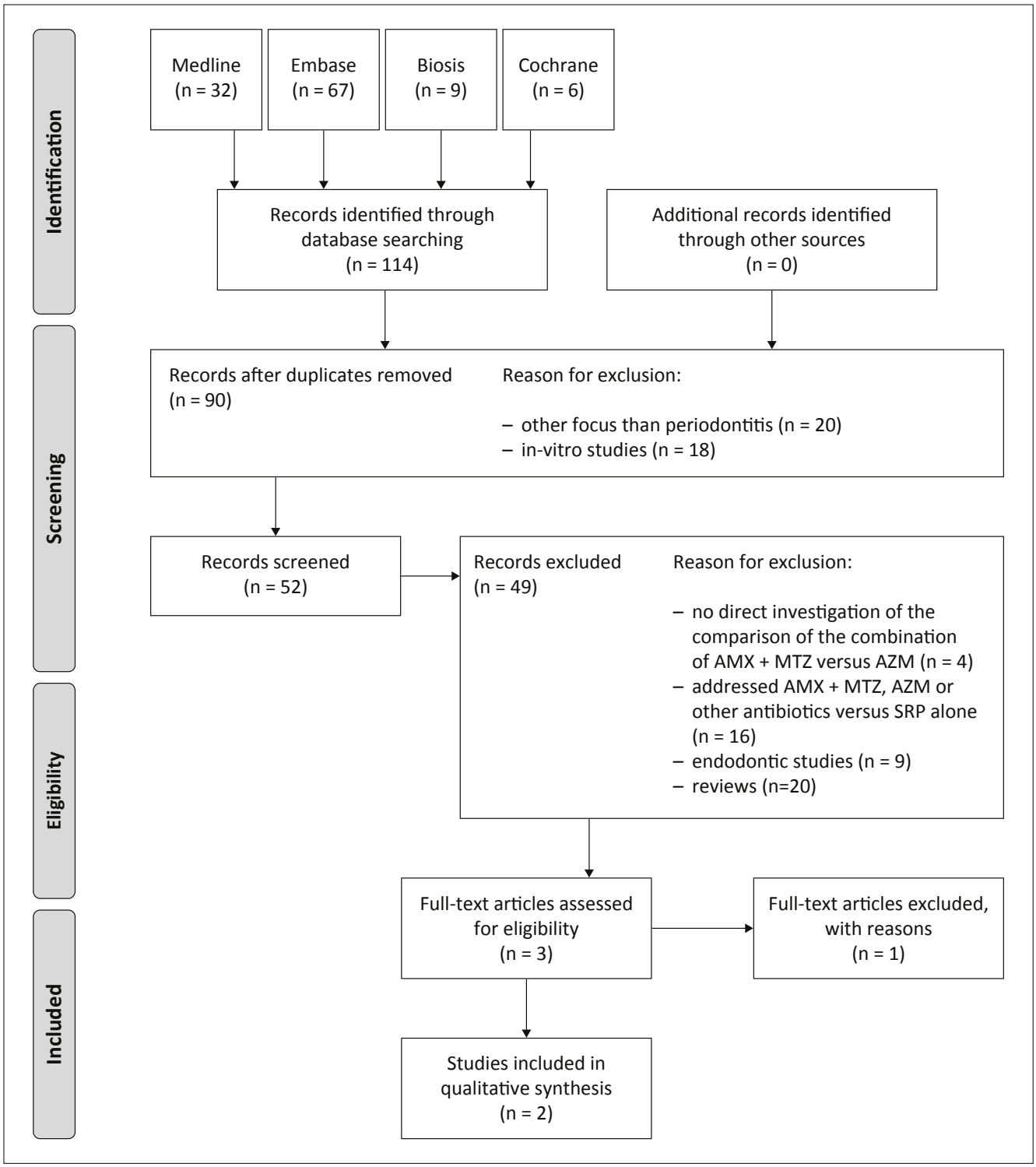

Fig. 1 PRISMA flowchart of the selection process of the included studies.

Results

Study selection

Search and screening

After applying the inclusion and exclusion criteria, only two studies finally matched the inclusion criteria (Saleh et al. 2016; Jentsch et al. 2016). All other studies had to be excluded either due to non-focus on periodontitis (n = 12), and did not directly investigate the comparison of the combination of AMX + MTZ versus AZM (n = 4), i.e. addressed AMX + MTZ, AZM or other antibiotics versus SRP alone (n = 12), represented in-vitro (n = 18) or endodontic studies (n = 9). The inter-rater agreement was found to be 100%. One adequately comparing the study investigated on the therapy retrospectively in aggressive periodontitis (AgP) cases and was also excluded (Ercan et al. 2015).

Summary of studies: characteristics (PICO)

Population

Description of studies

The main characteristics of the two included studies are summarised in Table I.

Tab. I Description of studies

Author	Jentsch 2015		Saleh 2016		
Type of periodontitis	chronic		chronic		
Type of study	prospective randomized clinical trial		single centre double blinded controlled randomized clinical trial		
Observation period	3 months and 12 months		3 months		
No. of measurements	6 sites		6 sites		
No. of patients	62		32		
Gender (m/f)	AZM	AMX + MTZ as control	AZM	AMX + MTZ	C
	13/16	18/13	4/8	4/9	5/7
Age (mean)	AZM	AMX + MTZ as control	AZM	AMX + MTZ	C
	54.66	53.48	56.3	52.1	56.1
Exclusion criteria for patients	AB the last 3 months AB the last 3 months periodontal treatment the last year pregnancy nursing smokers diabetes mellitus rheumatoid arthritis allergy against AB		AB the last 6 months periodontal treatment the last 6 months pregnant or lactating smokers uncontrolled diabetes cardiovascular diseases patients on warfarin anti-inflammatory drugs hypersensitivity to penicillin, MTZ or AZM aggressive periodontitis		
Type of antibiotics	AZM	AMX + MTZ	AZM	AMX + MTZ	
	500 mg 1×/d for 3d	AMX: 500 mg 3×/d MTZ: 400 mg 3×/d for 7d	500 mg 1×/d for 3d	AMX: 500 mg 3×/d MTZ: 200 mg 3×/d for 7d	

Intervention/comparison

In both studies, the patients' exclusion criteria were: smokers, pregnant women and patients who had no previous periodontal treatment nor periodontal treatment for the last six or twelve months, allergy against any of the selected antibiotics, systemic diseases and the use of any antibiotics in the previous three to six months. In both studies, six sites per tooth were measured. The number of patients varied from 32 (Saleh et al. 2016) to 62 (Jentsch et al. 2016) patients. Notably, there was a difference between the studies concerning dosages of the antibiotics (Tab. I), namely MTZ, which was prescribed either in a dosage of 200 mg (Saleh et al. 2016) or 400 mg (Jentsch et al. 2016). However, the intake period accounted for seven days in both studies, and the other antibiotics were used comparably.

Analysis of the risk of bias

The present study focused on a normal data distribution given in the paper of Saleh et al. (Saleh et al. 2016). The authors used adequate methods, the drop-out rate was low, and the randomization was computer-generated. Therefore, the study was classified as "low" risk of bias. The study of Jentsch et al. (Jentsch et al. 2016) had to be classified as "unclear" risk of bias study and no normal data distribution could be assumed. Both studies described had no blinding of the participants and personnel as well as no blinding of the outcome assessment.

Outcomes

Pocket depths

Table II depicts the extracted primary outcome parameters of interest, namely mean and median PD values at baseline and after three months. The calculated mean PDs for overall teeth and sites resulted in quite low PD values at baseline for the AMX + MTZ and AZM groups of 4.05 and 4.07 mm which was reported by Jentsch and co-workers (Jentsch et al. 2016). Similarly, the value declared was of 3.94 and 3.51 mm in the investigation carried out by Saleh et al. (Saleh et al. 2016). In both studies, these values significantly decreased to 2.90 and 2.88 mm for both groups (AMX + MTZ and AZM), which was reported by Jentsch and co-workers (Jentsch et al. 2016), whereas the value was 3.02 and 3.05 mm in the investigation by Saleh et al. (Saleh et al. 2016).

Tab. II Data extraction (mm PD) of the two included papers

Author		Jentsch 2015	Saleh 2016
n		29	11
AZM	BL	4.07 (median)	3.51 (mean)
	BL p5	3.72	
	BL p95	4.40	
	BL sd		0.34
	3M	2.88 (median)	3.05 (mean)
	3M p5	2.43	
	3M p95	3.32	
	3M sd		0.20
n		31	11
AMX + MTZ	BL	4.05 (median)	3.94 (mean)
	BL p5	3.43	
	BL p95	4.69	
	BL sd		0.70
	3M	2.90 (median)	3.02 (mean)
	3M p5	2.57	
	3M p95	3.45	
	3M sd		0.21

p: percentile, sd: standard deviation, BL: baseline, M: months

Discussion

This systematic review compared and investigated the combination of AMX + MTZ and AZM. It was analysed that better clinical results could be achieved with one of the respective regimens after non-surgical periodontal therapy of CP. The present systematic review included only two studies, which directly compared with both the antibiotics. In both regimens, comparable results were obtained in terms of PD reductions as an additive to SRP in the non-surgical adjunctive treatment of CP.

A recent meta-analysis (Keestra et al. 2015) also studied whole-mouth PD reductions after non-surgical periodontal therapy with different antibiotics. However, each antibiotic was compared versus placebo after three months and included no studies, which directly compared with one antibiotic against another. In this setting, they showed comparable mean reductions of –0.39 mm for AMX + MTZ and –0.36 mm for AZM, which was corroborated by the present study. In the latter meta-analysis (Keestra et al. 2015), data for AZM were, however, only available from one study including 32 patients (Emingil et al. 2012) and noteworthy, generalized AgP patients were assessed, which is in contrast to our review. More studies were identified evaluating AMX + MTZ, and eight studies with 248 patients were analysed. With regard to specific PDs, i.e. moderate (4–6 mm) and deep pockets (>6 mm), the mean difference of PD for AMX + MTZ accounted for –0.43 mm and –0.88 mm, respectively, when comparing – again – against placebo controls.

From other review reports on AZM, one study (Renatus et al. 2016) focused on the mean reductions of whole mouth PD for five studies. It was found that the PD reduction values in different studies and patient groups after three months were as follows: –0.88 mm in AgP patients (Emingil et al. 2012) and in CP patients –0.75 mm (Gomi et al. 2007), –0.72 mm and –0.77 mm (Oteo et al. 2010). Another meta-analysis reported the mean whole-mouth PD reductions of even twelve articles and reported a mean PD reduction of –0.99 mm (Zhang et al. 2016).

A higher mean PD reduction after SRP of up to 1.41 mm was found in a systematic review with adjunctive AMX + MTZ (Zandbergen et al. 2013). Results from a recent systematic review focusing on in-vitro efficacy with regard to the two antibiotics concluded that the combination of AMX + MTZ provided higher antimicrobial efficacy as compared to AZM. However, also in the present review, the number of available studies was low (Kaufmann et al. 2018), which did not allow for definitive conclusions, but corroborated the above-mentioned clinical data to some extent.

In this context, and as mentioned before, this systematic review included two studies only. The results should be therefore, interpreted with caution. Since, the study was calculated on a sample size that would have provided 80% power, which required 19 patients per treatment group, but, only 11 patients were included in both groups (Saleh et al. 2016). Also, the authors of that study pointed out that the results should be cautiously read.

Some methodological differences also make the two studies difficult to compare: whereas one study prescribed the antibiotics from the first day of SRP (Jentsch et al. 2016), the other investigation started after the last SRP session (Saleh et al. 2016). Obviously, the therapy plans influenced the time of antibiotic administration: whereas periodontal treatment was carried out in two to four sessions for each patient (approximately 90 minutes per session) (Saleh et al. 2016), participants of the other study received full-mouth SRP in two sessions, which were carried out within two consecutive days (Jentsch et al. 2016). In this context, a short-term research has directly compared with different time points of systemic antibiotic administration as adjuncts to SRP in the treatment of periodontitis (Griffiths et al. 2011).

In the present study, it was also aimed to assess the pocket closure and the probability of residual pockets using a proposed statistical approach (Kolakovic et al. 2014). Unfortunately, only one study qualified for this approach. Quite surprisingly, a PD reduction to less than 5 mm was only achieved in moderate pockets, whereas the probability of remaining pockets was almost 50% in deep pockets in both antibiotic groups. This is in contrast to the mentioned latter study, where the estimated risk for residual pockets >5 mm was 0 for both groups, i.e. placebo and antibiotic group.

Notably, these values are difficult to interpret, as the present study aimed to assess the probability of pocket closure (pockets ≤3 mm) or residual pockets ≥5 mm. Unfortunately, original data sets of the included studies were not available, even on request. Therefore, probability calculations of distinct threshold values were only possible for the one study, which reported on the mean values and standard deviations and analysed non-skewed data (Saleh et al. 2016):

In the case of residual PD ≤3 mm, probabilities of 7% and 6% for the combination of AMX + MTZ and 3% and 1% for AZM were found in moderate (4–6 mm) and deep (>6 mm) pockets,

Tab. III Clinical success probabilities (%) in Saleh et al. 2016

PD category		Baseline	Review
PD 4–6 mm			
	AMX + MTZ	0	7
	AZM	0	3
PD >6 mm			
	AMX + MTZ	0	6
	AZM	0	1
P (PD ≤3 mm): probability of having PD ≤3 mm after treatment			
PD category		**Baseline**	**Review**
PD 4–6 mm			
	AMX + MTZ	20	0
	AZM	8	0
PD >6 mm			
	AMX + MTZ	100	41
	AZM	100	47
P (PD ≥5 mm): probability of having PD ≥5 mm after treatment			

respectively. Based on these results, a resolution of the pockets to values ≤3 mm seems a difficult task. The calculated probability of residual pockets ≥5 mm accounted for 0% and 41% for AMX + MTZ and 0% and 47% for AZM in moderate (4–6 mm) and deep (>6 mm) pockets, respectively. This finding implies that a PD reduction to less than 5 mm was only achieved in moderate pockets. In contrast, the probability of remaining pockets was almost 50% in deep pockets in both antibiotic groups (see Tab. III).

Although the results of this study suggested some benefits for antibiotics intake during the active phase of the therapy, and these findings need to be confirmed by larger placebo-controlled RCTs with more extended follow-up periods, especially comparing both antibiotic regimens directly.

Conclusion

Within the limitations of the present review based on a small number of available studies, no definite conclusions can be drawn on the efficacy of the combination of AMX + MTZ versus AZM in the treatment of CP. Both regimens seem more or less to result in comparable PD reductions. From a clinical perspective, however, AZM may have some advantages, for example, with reference to treatment protocols and compliance. Based on the limited studies reported on the comparison of the two regimens, it is concluded that more RCTs in this context are necessary.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All relevant data supporting the conclusion of this article are within or mentioned in the manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding has been available other than that of the authors' institutions.

Authors' Contributions

PL and MK did the literature search and drafted the manuscript. CW verified the analytical methods, discussed the results and contributed to the final manuscript. TA validated the manuscript. DW helped with the statistical evaluation of the papers and the tables and participated in its design. PRS conceived the study and supervised the study as well as the literature search. All authors carefully read and approved the final text.

Zusammenfassung

Einleitung

Parodontitis ist durch Zahnfleischentzündung, Bildung von Zahnfleischtaschen, fortschreitender Attachmentverlust (AL) und Knochenschwund gekennzeichnet. Die Standardtherapie in einem ersten Schritt ist Scaling und Root Planing (SRP) (Badersten et al. 1981). Die Verwendung von zusätzlichen systemischen Antibiotika kann signifikante Vorteile bei der Verringerung der parodontalen Sondierungstiefe (PD), der Wiederherstellung des klinischen Attachments (CAL) sowie des Risikos eines weiteren Attachmentverlust (AL) bieten (Badersten et al. 1984). Das Ziel dieses systematischen Reviews war der Vergleich der Kombination von Amoxicillin und Metronidazol versus Azithromycin als zusätzliche systemische Antibiotika während der nicht chirurgischen paradontalen Therapie der chronischen Parodontitis.

Material und Methode

Die Studie wurde gemäss den PRISMA-Richtlinien für systematische Reviews durchgeführt. Vier Onlinedatenbanken (*Medline, Embase, Cochrane* und *Biosis*) wurden elektronisch durchsucht. Zusätzlich wurde bis zum 24. Oktober 2019 eine Handrecherche durchgeführt. Alle Volltexte, die die Einschlusskriterien erfüllten, wurden von zwei unabhängigen Forschern (PL und MK) bezüglich Bias bewertet. Die angewandte Methodik entspricht dem Cochrane-Collaboration-Standardschema für Bias. Die folgenden Daten wurden extrahiert: PD angegeben als Mittelwert oder Median zu Studienbeginn, einschliesslich der jeweiligen Standardabweichungen oder der 5- und 95-Perzentile. Sofern verfügbar, wurden die Daten nach drei oder sechs Monaten aufgenommen. Von 76 Studien konnten nur 2 Arbeiten in diese Analyse einbezogen werden.

Resultate

Die berechnete mittlere Wahrscheinlichkeit einer Sondierungstiefe (PD) von 3 mm nach nicht chirurgischer Parodontaltherapie in moderaten (4–6 mm) und tiefen (>6 mm) Taschen betrug 7% und 6% für die Kombination von Amoxicillin und Metronidazol. Für Azithromycin waren es 3% bzw. 1%. Die mittlere Wahrscheinlichkeit, dass Taschen ≤5 mm bestehen bleiben, lag bei moderaten Taschen mit beiden Antibiotika-Therapien bei 0, währenddessen bei tiefen Taschen bei Therapie

mit Amoxicillin und Metronidazol die Wahrscheinlichkeit für Resttaschen minim niedriger zu sein scheint.

Diskussion

Im Rahmen der vorliegenden Übersicht, die auf einer kleinen Anzahl verfügbarer Studien basiert, kann zugunsten der Patienten-Compliance und des Wohlbefindens der Patienten die Anwendung von Azithromycin als Ergänzung zur nicht chirurgischen parodontalen Therapie chronischer Parodontitis basiert auf der aktuellst bestehenden Literatur Amoxicillin und Metronidazol ersetzen. Beide Therapien scheinen mehr oder weniger zu vergleichbaren PD-Reduktionen zu führen.

Résumé

Introduction

La parodontite est caractérisée par l'inflammation des gencives, la formation de poches gingivales, une perte d'attache progressive (AL) et une perte osseuse. Dans un premier temps, le détartrage et le surfaçage radiculaire (*Scaling and Root Planing,* SRP) en constituent le traitement standard (Badersten et coll. 1981). L'antibiothérapie systémique complémentaire peut offrir des avantages significatifs en réduisant la profondeur de sondage parodontal (PD), en rétablissant l'attache clinique (CAL) et en limitant le risque de perte d'attache supplémentaire (AL) (Badersten et coll. 1984). Le but de cette revue systématique était de comparer l'administration de l'association amoxicilline + métronidazole à l'azithromycine en tant qu'antibiothérapie systémique complémentaire dans le cadre du traitement non chirurgical de la parodontite chronique.

Matériel et méthode

L'étude a été menée conformément aux lignes directrices PRISMA pour les revues systématiques. Quatre bases de données en ligne (Medline, Embase, Cochrane et Biosis) ont fait l'objet de recherches par voie informatique. De plus, une recherche manuelle a été effectuée jusqu'au 24 octobre 2019. Tous les textes intégraux répondant aux critères d'inclusion ont été évalués par deux chercheurs indépendants (PL et MK) en ce qui concerne leurs biais. La méthodologie utilisée était conforme au schéma standard de la Collaboration Cochrane en matière de biais. Les données suivantes ont été extraites : la PD indiquée en tant que valeur moyenne ou médiane au début de l'étude, y compris les écarts types respectifs ou les percentiles 5 et 95. Lorsque les données après trois ou six mois étaient disponibles, elles ont été prises en compte. Seules 2 études ont pu être retenues dans la présente analyse, sur un total de 76 études.

Résultats

La probabilité moyenne calculée d'une profondeur de sondage (PD) de 3 mm après traitement parodontal non chirurgical lors de poches modérées (4–6 mm) ou profondes (>6 mm) était respectivement de 7 % et 6 % pour l'association amoxicilline + métronidazole. Pour l'azithromycine, cette probabilité était de 3 % et 1 %. Pour les poches de profondeur modérée, la probabilité moyenne de poches résiduelles ≤5 mm était de 0 avec les deux traitements antibiotiques, alors que pour les poches profondes, la probabilité de poches résiduelles semble légèrement inférieure après traitement par amoxicilline + métronidazole.

Discussion

Dans le cadre de la présente analyse fondée sur un petit nombre d'études disponibles, l'administration d'azithromycine en tant que complément au traitement non chirurgical de la parodontite chronique peut remplacer le traitement par l'association amoxicilline + métronidazole, selon les données les plus récentes, en favorisant l'observance et le bien-être des patients. Les deux traitements semblent entraîner des réductions plus ou moins comparables de la PD.

Appendix

Tab. IV List of excluded studies. The reason for exclusion was arranged in the following categories: review (for reviews), endo (for endodontic studies), other (for studies not addressing the research question), in-vitro (for in-vitro studies) or clin (for clinical studies) and no comparison (for studies only reporting about one or two of the three antibiotics and not conducting any comparison between AMX/MTZ and AZM).

	Reference	Category	Exclusion criteria
1)	Abazi & Mihani 2018	clin	prescription of antibiotics for periodontal disease among dentists in the region of Tirana
2)	Acharya et al. 2018	clin	focus on pharmacovigilance in a medical intensive care unit
3)	Alattas & Alyami 2017	endo	reporting about prescription of antibiotics usus in southern Saudi Arabia focusing endodontic pathology
4)	Amerio et al. 2019	review	review focusing on the degree of compliance with supportive periodontal therapy
5)	Antunes et al. 2019	other	commentary on noninferiority trials in oral medicine
6)	Arias-Bujanda et al. 2019	review	systematic review and meta-analysis on the accuracy of single molecular biomarkers in gingival crevicular fluid
7)	Arora et al. 2017	review	review, no comparison of AMX-MTZ and AZM
8)	Barbosa-Ribeiro et al. 2016	endo	focusing on antimicrobial susceptibility after failure of endodontic treatment
9)	Bartold et al. 2013	no comparison	focusing only on AZM

Tab. IV List of excluded studies. The reason for exclusion was arranged in the following categories: review (for reviews), endo (for endodontic studies), other (for studies not addressing the research question), in-vitro (for in-vitro studies) or clin (for clinical studies) and no comparison (for studies only reporting about one or two of the three antibiotics and not conducting any comparison between AMX/MTZ and AZM).

	Reference	Category	Exclusion criteria
10)	Belibasakis & Thurnheer 2014	in-vitro	in-vitro study
11)	Bhat et al. 2019	in-vitro	in-vitro study
12)	Brook 2013	other	focus on head and neck infections in general rather than periodontal aspects, not addressing research question
13)	Brook 2015	other	focus on head and neck infections in general rather than periodontal aspects, not addressing research question
14)	Carrasco et al. 2000	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
15)	Chopra et al. 2015	other	focus on cutaneous adverse drug reactions, not addressing research question
16)	Coulaud 1995	no comparison	focusing only on AZM
17)	Dakic et al. 2016	clin	AZM was not tested, systematic review and meta-analysis
18)	Dar-Odeh et al. 2018	clin	review focusing on prescribing of antibiotics for oro-facial infections in paediatric outpatient
19)	Ercan et al. 2015	clin	clinical study, patients with aggressive periodontitis
20)	Fadare et al. 2017	clin	focusing on inappropriate prescribing of medicines among dentists in a hospital dental clinic in Nigeria
21)	Feik et al. 2001	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
22)	Fresnadillo Martinez et al. 1997	review	clinical study about the current state of antibiotics in odontogene infections in general
23)	Garg et al. 2014	other	survey, not addressing research question
24)	Georgiou et al. 2019	review	systematic review and meta-analysis on the association of periodontitis and elevated concentrations of inflammatory mediators in peripheral blood
25)	Greenstein 2004	no comparison	clinical study
26)	Harris & Harris 2015	other	focus on HSV-1 and Alzheimer disease, not addressing research question
27)	Hernández-Rizzo 2003	review	in-vitro review, full text was not available until data
28)	Herrera et al. 2012	review	clinical study
29)	Isla et al. 2008	other	focus on odontogenic infections in general rather than periodontitis, not addressing research question
30)	Jacinto et al. 2003	endo	focus on analysis of infected root canals
31)	Japoni et al. 2011	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
32)	Jaramillo et al. 2005	other	clin and in-vitro, but focus on abscesses, not addressing research question
33)	Jentsch et al. 2016	clin	clinical study
34)	Kaufmann et al. 2018	review	in-vitro review
35)	Keestra et al. 2015	review	clinical systematic review and meta-analysis but no comparison of the antibiotics AMX-MTZ and AZM
36)	Kuriyama et al. 2007	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
37)	Kuruvilla & De la Morena 2013	other	focus on primary immune deficiency disorders, not addressing research question
38)	Lafuente Ibanez de Mendoza et al. 2019	review	systematic review on the role of Pg in oral squamous cell carcinoma development
39)	Leszczyńska et al. 2011	review	updated review, focus on periodontal pharmacotherapy in general

Tab. IV List of excluded studies. The reason for exclusion was arranged in the following categories: review (for reviews), endo (for endodontic studies), other (for studies not addressing the research question), in-vitro (for in-vitro studies) or clin (for clinical studies) and no comparison (for studies only reporting about one or two of the three antibiotics and not conducting any comparison between AMX/MTZ and AZM).

	Reference	Category	Exclusion criteria
40)	Liaw et al. 2019	clin	clinical study, only 2-months data
41)	Liu et al. 2009	other	focus on vaccines and PDT
42)	Loesche 1999	review	critical review, focus on antimicrobial treatment of periodontal disease
43)	Maestre et al. 2007	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
44)	Mahajan et al. 2012	endo	focus on management of endodontic infections
45)	Mattina 2007	other	focus on Clarithromycin, not addressing research question
46)	McGowan 2018	clin	AZM was not tested, systematic review and meta-analysis of RCTs
47)	Mínguez et al. 2019	in-vitro	in-vitro study
48)	Mouratidou et al. 2011	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
49)	Muniz et al. 2013	review	focusing only on AZM
50)	Murillo 2003	clin	focus on orofacial infections, not addressing research question
51)	NCT 2018	clin	clinical study, the combination of the antibiotics AMX + MTZ was not tested
52)	Ong et al. 2017	in-vitro	in-vitro study
53)	Ong et al. 2019	other	focusing on prescribing trends of systemic antibiotics by periodontists in Australia via online questionnaire
54)	Paju et al. 2007	other	focus on coronary events, not addressing research question
55)	Palappallil et al. 2017	other	focus on adverse drug reactions, not addressing research question
56)	Papathanasiou et al. 2016	other	a survey of periodontists in the US, not addressing research question
57)	Parenti et al. 2015	review	narrative review with focus on endothelial dysfunction
58)	Parnham 2011	other	focus on immunology in general, not addressing research question
59)	Rams et al. 2014	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
60)	Ramu & Padmanabhan 2012	review	practice review on antibiotic prophylaxis
61)	Ranganathan et al. 2015	review	clinical review with focus on summarizing factors to be considered while administering systemic antibiotics as an adjunct to mechanical debridement
62)	Rolim De Sousa et al. 2003	endo	bacteriological study of root canals associated with periapical abscesses
63)	Ryan 2005	other	general describing study of non-surgical approaches of the treatment of periodontal disease, not addressing research question
64)	Saleh et al. 2016	clin	clinical study, patients with chronic periodontitis
65)	Santos et al. 2015	review	focus on diabetic patients, systematic review
66)	Saquib et al. 2019	in-vitro	in-vitro study
67)	Segura-Egea et al. 2010	endo	focus on management of endodontic infections amongst Spanish oral surgeons
68)	Serrano et al. 2009	other	focus on antibiotic resistance of periodontal pathogens, not addressing research question
69)	Sgolastra et al. 2014	review	AZM was not tested, systematic review and meta-analysis
70)	Shannon et al. 2011	other	focus on Bisphosphonates and osteonecrosis of the jaw, not addressing research question
71)	Siqueira & Rôças 2013	endo	focus on endodontic abscesses
72)	Slots et al. 2004	review	description of systemic antibiotics in periodontics in general, not specifically in vitro

Tab. IV List of excluded studies. The reason for exclusion was arranged in the following categories: review (for reviews), endo (for endodontic studies), other (for studies not addressing the research question), in-vitro (for in-vitro studies) or clin (for clinical studies) and no comparison (for studies only reporting about one or two of the three antibiotics and not conducting any comparison between AMX/MTZ and AZM).

	Reference	Category	Exclusion criteria
73)	Soares et al. 2015	in-vitro	in-vitro study
74)	Somma et al. 2011	endo	focus on endo and general health
75)	Sousa et al. 2013	endo	focus on antimicrobial susceptibility pattern of infected root canals
76)	Souto et al. 2018	clin	focus on diabetic subjects, systematic review and meta-analysis
77)	Suda et al. 2018	other	focus on antibiotic prophylaxis for tooth extractions, dental implants and peri-odontal surgical procedures
78)	Sweeny et al. 2004	other	focus on antibiotic resistance in the dental practice, not addressing research question
79)	Tarullo et al. 2001	no comparison	focus on Helicobacter pylori, no comparison of AMX + MTZ and AZM
80)	Teughels et al. 2014	review	clinical study, patients with aggressive periodontitis
81)	Tomas et al. 2007	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
82)	Van den Wyngaert et al. 2007	other	focus on osteonecrosis of the jaw and bisphosphonates, not addressing research question
83a), 83b)	Van Winkelhoff et al. 1999, Van Winkelhoff et al. 2000	in-vitro	double listed, the combination of the antibiotics AMX + MTZ was not tested
84)	Van Winkelhoff et al. 2005	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
85)	Veloo et al. 2012	in-vitro	the combination of the antibiotics AMX + MTZ was not tested
86)	Voils et al. 2005	clin	clinical study, AMX was not tested
87)	Wang 2018	clin	AZM was not tested
88)	Zandbergen et al. 2013	clin	AZM was not tested, systematic review
89)	Zhang et al. 2016	clin	the combination of the antibiotics AMX + MTZ was not tested, meta-analysis of RCTs

References

Abazi B, Mihani J: Prescription of antibiotics for periodontal disease among dentists in the region of tirana. Open Access Maced J Med Sci 6: 1486–1491 (2018)

Acharya T, Trivedi M, Vekariya R, Chhaiya S, Mehta D: Pharmacovigilance study of patients receiving treatment at medical icu of c. U. Shah medical college & hospital, surendranagar. Int J Pharm Sci Res 9: 5265–5270 (2018)

Alattas H A, Alyami S H: Prescription of antibiotics for pulpal and periapical pathology among dentists in southern saudi arabia. J Glob Antimicrob Resist 9: 82–84 (2017)

Amerio E, Mainas G, Petrova D, Giner Tarrida L, Nart J, Monje A: Compliance with supportive periodontal/peri-implant therapy: A systematic review. J Clin Periodontol 28: 28 (2019)

Antunes J L F, Domaneschi C, Lemos C A: Noninferiority trials in oral medicine. Oral Dis 25: 357–362 (2019)

Arias-Bujanda N, Regueira-Iglesias A, Balsa-Castro C, Nibali L, Donos N, Tomas I: Accuracy of single molecular biomarkers in gingival crevicular fluid for the diagnosis of periodontitis: A systematic review and meta-analysis. J Clin Periodontol 24: 24 (2019)

Arora A, Khattri S, Ismail N M, Kumbargere Nagraj S, Prashanti E: School dental screening programmes for oral health. Cochrane Database Syst Rev 12: CD012595 (2017)

Badersten A, Nilvéus R, Egelberg J: Effect of nonsurgical periodontal therapy. I. Moderately advanced periodontitis. J Clin Periodontol 8: 57–72 (1981)

Badersten A, Nilveus R, Egelberg J: Effect of nonsurgical periodontal therapy. Ii. Severely advanced periodontitis. J Clin Periodontol 11: 63–76 (1984)

Barbosa-Ribeiro M, De-Jesus-Soares A, Zaia A A, Ferraz C C R, Almeida J F A, Gomes B P F A: Antimicrobial susceptibility and characterization of virulence genes of enterococcus faecalis isolates from teeth with failure of the endodontic treatment. J Endod 42: 1022–1028 (2016)

Bartold P M, du Bois A H, Gannon S, Haynes D R, Hirsch R S: Antibacterial and immunomodulatory properties of azithromycin treatment implications for periodontitis. Inflammopharmacology 21: 321–338 (2013)

Belibasakis G N, Thurnheer T: Validation of antibiotic efficacy on in vitro subgingival biofilms. J Periodontol 85: 343–348 (2014)

Bhat K G, Khot P, Patil S, Pattar G, Majukar S: Antimicrobial susceptibility pattern of oral isolates of aggregatibacter actinomycetemcomitans. J Oral Maxillofac Pathol 23: 231–235 (2019)

Brook I: Fusobacterial infections in children. Curr Infect Dis Rep 15: 288–294 (2013)

Brook I: Fusobacterial head and neck infections in children. Int J Pediatr Otorhinolaryngol 79: 953–958 (2015)

Buset S L, Zitzmann N U, Weiger R, Walter C: Nonsurgical periodontal therapy supplemented with systemically administered azithromycin: A systematic review of rcts. Clin Oral Investig 19: 1763–1775 (2015)

Carrasco E, Martinez M, Calbacho M, Wilckens M: In vitro activity of amoxicillin, tetracyclines, azithromycin, ofloxacin and metronidazole against porphyromonas gingivalis, prevotella intermedia and fusobacterium nucleatum strains. Anaerobe 5: 443–445 (2000)

Chopra D, Sharma V, Kapoor R, Dwivedi S: An observational study of cutaneous adverse drug reactions in a teaching hospital. Int J Clin Pharm 37: 996–999 (2015)

Coulaud J P: Azithromyin: New trends. Pathol Biol (Paris) 43: 547–550 (1995)

Dakic A, Boillot A, Colliot C, Carra M C, Czernichow S, Bouchard P: Detection of porphyromonas gingivalis and aggregatibacter actinomycetemcomitans after systemic administration of amoxicillin plus metronidazole as an adjunct to non-surgical periodontal therapy: A systematic review and meta-analysis. Front Microbiol 7: 1277 (2016)

Dar-Odeh N, Fadel H T, Abu-Hammad S, Abdeljawad R, Abu-Hammad O A: Antibiotic prescribing for oro-facial infections in the paediatric outpatient: A review. Antibiotics 7: 25 (2018)

Emingil G, Han B, Ozdemir G, Tervahartiala T, Vural C, Atilla G, Baylas H, Sorsa T: Effect of azithromycin, as an adjunct to nonsurgical periodontal treatment, on microbiological parameters and gingival crevicular fluid biomarkers in generalized aggressive periodontitis. J Periodontal Res 47: 729–739 (2012)

Ercan E, Uzun B C, Ustaoglu G: Effects of azithromycin versus metronidazole-amoxicillin combination as an adjunct to nonsurgical periodontal therapy of generalized aggressive periodontitis. Niger J Clin Pract 18: 506–510 (2015)

Fadare J O, Oshikoya K A, Obimakinde O S, Sijuade A O, Afolayan J M, Adeleke A A, Godman B, Ojumu D O: Patterns of drugs prescribed for dental outpatients in nigeria: Findings and implications. Acta Odontol Scand 75: 496–506 (2017)

Feik D, Mortensen J E, Rhoads S L, Egleton J, Rams T E: Antibiotic susceptibility profile of periodontal streptococcus constellatus. Abstr Gen Meet Am Soc Microbiol 101: 3–4 (2001)

Forrest J L, Miller S A: Evidence-based decision making in action: Part 1 – finding the best clinical evidence. J Contemp Dent Pract 3: 10–26 (2002)

Fresnadillo Martinez M J, Blaquez de Castro A M, Garcia Sanchez E, Garcia Sanchez J E, Garcia Rodriguez J A: The current state and perspectives on antibiotic treatment for odontogene infections. Rev Esp Quimio 10: 203–211 (1997)

Garg A K, Agrawal N, Tewari R K, Kumar A, Chandra A: Antibiotic prescription pattern among indian oral healthcare providers: A cross-sectional survey. J Antimicrob Chemother 69: 526–528 (2014)

Georgiou A C, Crielaard W, Armenis I, de Vries R, van der Waal S V: Apical periodontitis is associated with elevated concentrations of inflammatory mediators in peripheral blood: A systematic review and meta-analysis. J Endod 18: 18 (2019)

Gomi K, Yashima A, Iino F, Kanazashi M, Nagano T, Shibukawa N, Ohshima T, Maeda N, Arai T: Drug concentration in inflamed periodontal tissues after systemically administered azithromycin. J Periodontol 78: 918–923 (2007)

Greenstein G: Efficacy of subantimicrobial-dose doxycycline in the treatment of periodontal diseases: A critical evaluation. Int J Periodontics Restorative Dent 24: 528–543 (2004)

Griffiths G S, Ayob R, Guerrero A, Nibali L, Suvan J, Moles D R, Tonetti M S: Amoxicillin and metronidazole as an adjunctive treatment in generalized aggressive periodontitis at initial therapy or re-treatment: A randomized controlled clinical trial. J Clin Periodontol 38: 43–49 (2011)

Harris S A, Harris E A: Herpes simplex virus type 1 and other pathogens are key causative factors in sporadic alzheimer's disease. J Alzheimers Dis 48: 319–353 (2015)

Hauri D, Schmidlin P R, Puhan M A: Development of an easily interpretable presentation format for meta-analyses in periodontal surgery. Evid Based Dent 9: 89–90 (2008)

Hernández-Rizzo G A: Usefulness of antimicrobial agents in periodontal disease. Informe Medico 5: 97–100 (2003)

Herrera D, Matesanz P, Bascones-Martinez A, Sanz M: Local and systemic antimicrobial therapy in periodontics. J Evid Based Dent Pract 12: 50–60 (2012)

Isla A, Canut A, Rodriguez-Gascon A, Planells P, Beltri-Orta P, Salmeron-Escobar J I, Labora A, Pedraz J L: [Antibiotic therapy in odontogenic infections in children and adolescents: Pharmacokinetic/pharmacodynamic analysis]. Enferm Infecc Microbiol Clin 26: 621–628 (2008)

Jacinto R C, Gomes B P F A, Ferraz Ccr, Zaia A A, Souza Filho F J: Microbiological analysis of infected root canals from symptomatic and asymptomatic teeth with periapical periodontitis and the antimicrobial susceptibility of some isolated anaerobic bacteria. Oral Microbiol Immunol 18: 285–292 (2003)

Japoni A, Vasin A, Noushadi S, Kiany F, Japoni S, Alborzi A: Antibacterial susceptibility patterns of porphyromonas gingivalis isolated from chronic periodontitis patients. Med Oral Patol Oral Cir Bucal 16: e1031–1035 (2011)

Jaramillo A, Arce R M, Herrera D, Betancourth M, Botero J E, Contreras A: Clinical and microbiological characterization of periodontal abscesses. J Clin Periodontol 32: 1213–1218 (2005)

Jentsch Hfr, Buchmann A, Friedrich A, Eick S: Nonsurgical therapy of chronic periodontitis with adjunctive systemic azithromycin or amoxicillin/metronidazole. Clin Oral Investig 20: 1765–1773 (2016)

Kaufmann M, Lenherr P, Walter C, Thurnheer T, Attin T, Wiedemeier D B, Schmidlin P R: Comparing the antimicrobial in vitro efficacy of amoxicillin/metronidazole against azithromycin – a systematic review. Dent J (Basel) 6: (2018)

Keestra Jaj, Grosjean I, Coucke W, Quirynen M, Teughels W: Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: A systematic review and meta-analysis. J Periodontal Res 50: 294–314 (2015)

Kolakovic M, Held U, Schmidlin P R, Sahrmann P: An estimate of pocket closure and avoided needs of surgery after scaling and root planing with systemic antibiotics: A systematic review. BMC Oral Health 14: 159 (2014)

Kuriyama T, Williams D W, Yanagisawa M, Iwahara K, Shimizu C, Nakagawa K, Yamamoto E, Karasawa T: Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. Oral Microbiol Immunol 22: 285–288 (2007)

Kuruvilla M, de la Morena M T: Antibiotic prophylaxis in primary immune deficiency disorders. J Allergy Clin Immunol Pract 1: 573–582 (2013)

Lafuente Ibanez de Mendoza I, Maritxalar Mendia X, Garcia de la Fuente A M, Quindos Andres G, Aguirre Urizar J M: Role of porphyromonas gingivalis in oral squamous cell carcinoma development: A systematic review. J Periodontal Res 55: 13–22 (2020)

Leszczyńska A, Buczko P, Buczko W, Pietruska M: Periodontal pharmacotherapy – an updated review. Adv Med Sci 56: 123–131 (2011)

Liaw A, Miller C, Nimmo A: Comparing the periodontal tissue response to non-surgical scaling and root planing alone, adjunctive azithromycin, or adjunctive amoxicillin plus metronidazole in generalized chronic moderate-to-severe periodontitis: A preliminary randomized controlled trial. Aust Dent J 64: 145–152 (2019)

Liu P F, Zhu W H, Huang C M: Vaccines and photodynamic therapies for oral microbial-related diseases. Curr Drug Metab 10: 90–94 (2009)

Loesche W J: The antimicrobial treatment of periodontal disease: Changing the treatment paradigm. Crit Rev Oral Biol Med 10: 245–275 (1999)

Maestre J R, Bascones A, Sanchez P, Matesanz P, Aguilar L, Gimenez M J, Perez-Balcabao I, Granizo J J, Prieto J: Odontogenic bacteria in periodontal disease and resistance patterns to common antibiotics used as treatment and prophylaxis in odontology in spain. Rev Esp Quimioter 20: 61–67 (2007)

Mahajan A, Sharma V, Vats A, Srivastav A: Pattern of antibiotic prescription in the management of endodontic infections amongst oral and maxillofacial surgeons and endodontists in gujarat. Indian J Public Health Res Dev 3: 1–3 (2012)

Mattina R: Clarithromycin in dental infections. Trends in Medicine 7: 71–80 (2007)

McGowan K: Insufficient evidence to compare the efficacy of treatments for medication-related osteonecrosis of the jaws. J Evid Based Dent Pract 18: 70–72 (2018)

Mínguez M, Ennibi O K, Perdiguero P, Lakhdar L, Abdellaoui L, Sánchez M C, Sanz M, Herrera D: Antimicrobial susceptibilities of aggregatibacter actinomycetemcomitans and porphyromonas gingivalis strains from periodontitis patients in morocco. Clin Oral Investig 23: 1161–1170 (2019)

Mouratidou A, Karbach J, D'Hoedt B, Al-Nawas B: Antibiotic susceptibility of cocultures in polymicrobial infections such as peri-implantitis or periodontitis: An in vitro model. J Periodontol 82: 1360–1366 (2011)

Muniz F W M G, de Oliveira C C, de Sousa Carvalho R, Moreira M M S M, de Moraes M E A, Martins R S: Azithromycin: A new concept in adjuvant treatment of periodontitis. Eur J Pharmacol 705: 135–139 (2013)

Murillo J: Treatment of bacterial orofacial infections. Med Oral 8: 154 (2003)

NCT: Efficacy of azithromycin as an adjunct to non-surgical periodontal treatment. https://clinicaltrialsgov/show/NCT03629288 (2018)

Ong A, Kim J, Loo S, Quaranta A, Rincon A J: Prescribing trends of systemic antibiotics by periodontists in australia. J Periodontol 90: 982–992 (2019)

Ong H S, Oettinger-Barak O, Dashper S G, Darby I B, Tan K H, Reynolds E C: Effect of azithromycin on a red complex polymicrobial biofilm. J Oral Microbiol 9: 1339579 (2017)

Oteo A, Herrera D, Figuero E, O'Connor A, Gonzalez I, Sanz M: Azithromycin as an adjunct to scaling and root planing in the treatment of porphyromonas gingivalis-associated periodontitis: A pilot study. J Clin Periodontol 37: 1005–1015 (2010)

Paju S, Sinisalo J, Pussinen P J, Valtonen V, Nieminen M S: Is periodontal infection behind the failure of antibiotics to prevent coronary events? Atherosclerosis 193: 193–195 (2007)

Palappallil D S, Ramnath S N, Gangadhar R: Adverse drug reactions: Two years' experience from a tertiary teaching hospital in kerala. Natl J Physiol Pharm Pharmacol 7: 403–411 (2017)

Papathanasiou E, Finkelman M, Hanley J, Parashis A O: Prevalence, etiology and treatment of peri-implant mucositis and peri-implantitis: A survey of periodontists in the united states. J Periodontol 87: 493–501 (2016)

Parenti A, Paccosi S, Cairo F, Defraia E: Treatment of periodontitis for the prevention of endothelial dysfunction: A narrative review. Curr Vasc Pharmacol 13: 749–758 (2015)

Parnham M J: Immunomodulatory approaches to the treatment of infections. Infektoloski Glasnik 31: 15–27 (2011)

Position paper: Systemic antibiotics in periodontics. J Periodontol 75: 1553–1565 (2004)

Rams T E, Feik D, Mortensen J E, Degener J E, van Winkelhoff A J: Antibiotic susceptibility of periodontal streptococcus constellatus and streptococcus intermedius clinical isolates. J Periodontol 85: 1792–1798 (2014)

Ramu C, Padmanabhan T V: Indications of antibiotic prophylaxis in dental practice–review. Asian Pac J Trop Biomed 2: 749–754 (2012)

Ranganathan A T, Gita B, Ramya V: Role of systemic antibiotics in the management of periodontal diseases. Biomed Pharmacol J 8SE: 691–694 (2015)

Renatus A, Herrmann J, Schönfelder A, Schwarzenberger F, Jentsch H: Clinical efficacy of azithromycin as an adjunctive therapy to non-surgical periodontal treatment of periodontitis: A systematic review and meta-analysis. J Clin Diagn Res 10: ZE01–7 (2016)

Rolim de Sousa E L, Randi Ferraz C C, Figueiredo de Almeida Gomes B P, Tavares Pinheiro E, Batista Teixeira F, de Souza–Filho F J: Bacteriological study of root canals associated with periapical abscesses. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96: 332–339 (2003)

Ryan M E: Nonsurgical approaches for the treatment of periodontal diseases. Dent Clin North Am 49: 611–636 (2005)

Saleh A, Rincon J, Tan A, Firth M: Comparison of adjunctive azithromycin and amoxicillin/metronidazole for patients with chronic periodontitis: Preliminary randomized control trial. Aust Dent J 61: 469–481 (2016)

Santos C M M L, Lira R, Fischer R G, Santos A P P, Oliveira B H: Systemic antibiotics in periodontal treatment of diabetic patients: A systematic review. PLoS ONE 10: (2015)

Saquib S A, AlQahtani N A, Ahmad I, Kader M A, Al Shahrani S S, Asiri E A: Evaluation and comparison of antibacterial efficacy of herbal extracts in combination with antibiotics on periodontal pathobionts: An in vitro microbiological study. Antibiotics 8: (2019)

Segura–Egea J J, Velasco–Ortega E, Torres–Lagares D, Velasco–Ponferrada M C, Monsalve–Guil L, Llamas–Carreras J M: Pattern of antibiotic prescription in the management of endodontic infections amongst spanish oral surgeons. Int Endod J 43: 342–350 (2010)

Serrano C, Torres N, Valdivieso C, Castano C, Barrera M, Cabrales A: Antibiotic resistance of periodontal pathogens obtained from frequent antibiotic users. Acta Odontol Latinoam 22: 99–104 (2009)

Sgolastra F, Severino M, Petrucci A, Gatto R, Monaco A: Effectiveness of metronidazole as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A systematic review and meta-analysis. J Periodontal Res 49: 10–19 (2014)

Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L A, PRISMA-P Group: Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ 350: g7647 (2015)

Shannon J, Shannon J, Modelevsky S, Grippo A A: Bisphosphonates and osteonecrosis of the jaw. J Am Geriatr Soc 59: 2350–2355 (2011)

Siqueira J F, Rôças I N: Microbiology and treatment of acute apical abscesses. Clin Microbiol Rev 26: 255–273 (2013)

Soares Gms, Teles F, Starr J R, Feres M, Patel M, Martin L, Teles R: Effects of azithromycin, metronidazole, amoxicillin, and metronidazole plus amoxicillin on an in vitro polymicrobial subgingival biofilm model. Antimicrob Agents Chemother 59: 2791–2798 (2015)

Somma F, Castagnola R, Bollino D, Marigo L: Oral inflammatory process and general health part 2: How does the periapical inflammatory process compromise general health? Eur Rev Med Pharmacol Sci 15: 35–51 (2011)

Sousa E L R, Gomes B P F A, Jacinto R C, Zaia A A, Ferraz C C R: Microbiological profile and antimicrobial susceptibility pattern of infected root canals associated with periapical abscesses. Eur J Clin Microbiol Infect Dis 32: 573–580 (2013)

Souto M L S, Rovai E S, Ganhito J A, Holzhausen M, Chambrone L, Pannuti C M: Efficacy of systemic antibiotics in nonsurgical periodontal therapy for diabetic subjects: A systematic review and meta-analysis. Int Dent J 68: 207–220 (2018)

Suda K J, Henschel H, Patel U, Fitzpatrick M A, Evans C T: Use of antibiotic prophylaxis for tooth extractions, dental implants, and periodontal surgical procedures. Open Forum Infect Dis 5: (2018)

Sweeny L C, Dave J, Chambers P A, Heritage J: Antibiotic resistance in general dental practice – a cause for concern? J Antimicrob Chemother 53: 567–576 (2004)

Tarullo A, Tattoli M, Cagiano R: Persistent eradication of helicobacter pylori after systemic politherapy associated with periodontal pockets treatment with metronidazole and calcium sulphate. Eur Rev Med Pharmacol Sci 5: 127–129 (2001)

Team R C: R: A language and environment for statistical computing. Vienna, austria: R foundation for statistical computing. Available: Http. www R-project org [accessed 20 January 2015] (2015)

Teughels W, Dhondt R, Dekeyser C, Quirynen M: Treatment of aggressive periodontitis. Periodontol 2000 65: 107–133 (2014)

Tomas I, Tomas M, Alvarez M, Velasco D, Potel C, Limeres J, Diz P: Susceptibility of oral obligate anaerobes to telithromycin, moxifloxacin and a number of commonly used antibacterials. Oral Microbiol Immunol 22: 298–303 (2007)

Van den Wyngaert T, Huizing M T, Vermorken J B: Osteonecrosis of the jaw related to the use of bisphosphonates. Curr Opin Oncol 19: 315–322 (2007)

van Winkelhoff A J, Herrera D, Winkel E G, Dellemijn–Kippuw N, Vandenbroucke–Grauls C M, Sanz M: [Antibiotic resistance in the subgingival microflora in patients with adult periodontitis. A comparative survey between Spain and the Netherlands]. Ned Tijdschr Tandheelkd 106: 290–294 (1999)

van Winkelhoff A J, Herrera Gonzales D, Winkel E G, Dellemijn–Kippuw N, Vandenbroucke–Grauls C M, Sanz M: Antimicrobial resistance in the subgingival microflora in patients with adult periodontitis. A comparison between the netherlands and spain. J Clin Periodontol 27: 79–86 (2000)

van Winkelhoff A J, Herrera D, Oteo A, Sanz M: Antimicrobial profiles of periodontal pathogens isolated from periodontitis patients in the netherlands and spain. J Clin Periodontol 32: 893–898 (2005)

Veloo A C M, Seme K, Raangs E, Rurenga P, Singadji Z, Wekema–Mulder G, van Winkelhoff A J: Antibiotic susceptibility profiles of oral pathogens. Int J Antimicrob Agents 40: 450–454 (2012)

Voils S A, Evans M E, Lane M T, Schosser R H, Rapp R P: Use of macrolides and tetracyclines for chronic inflammatory diseases. Ann Pharmacother 39: 86–94 (2005)

Wang J C: The use of amoxicillin (500 mg) plus metronidazole (500 mg) for 7 days adds adjunctive benefits for nonsurgical periodontal therapy, but limited evidence supports higher/longer dose. J Evid Based Dent Pract 18: 249–251 (2018)

Zandbergen D, Slot D E, Cobb C M, Van der Weijden F A: The clinical effect of scaling and root planing and the concomitant administration of systemic amoxicillin and metronidazole: A systematic review. J Periodontol 84: 332–351 (2013)

Zeng X, Zhang Y, Kwong J S, Zhang C, Li S, Sun F, Niu Y, Du L: The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. J Evid Based Med 8: 2–10 (2015)

Zhang Z, Zheng Y, Bian X: Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: A meta-analysis of randomized controlled clinical trials. J Periodontal Res 51: 275–283 (2016)